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ORIGINAL RESEARCH

Glycemic Control in Chinese Patients with Type 2 Diabetes Mellitus Receiving Oral Antihyperglycemic Medication-Only or Insulin-Only Treatment: A Cross-Sectional Survey

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ABSTRACT

Introduction: The primary aim of this analysis was to explore whether glycemic control (glycated hemoglobin [HbA1c] <7%) and the incidence of hypoglycemia are different between Chinese patients with type 2 diabetes mellitus (T2DM) receiving oral antihyperglycemic medication (OAM)-only or insulin-only regimens.

Methods: Physicians in nine Chinese cities completed surveys (Adelphi Real World Diabetes Disease Specific Programme) from October 2011 to March 2012. Key information collected included patients' demographic and clinical characteristics, HbA1c levels, and hypoglycemia incidence. Patients receiving OAM-only ($n = 1077$) or insulin-only ($n = 292$) regimens for ≥6 months who had most recent HbA1c results available and measured within 3 months of survey completion were included. The primary and secondary outcomes were glycemic control and the incidence of hypoglycemia. Primary (multivariate logistic regression analysis with adjustment for potential confounders) and sensitivity analyses (propensity score matching method) were performed.

Results: A higher proportion of patients in the insulin-only group achieved glycemic control than patients in the OAM-only group (41.8% vs 35.9%). Insulin-only treatment was associated with significantly ($P = 0.013$) better glycemic control than OAM-only treatment (odds ratio [95% confidence interval]: 1.48 [1.09, 2.01]). A higher proportion of patients in the insulin-only group experienced hypoglycemia (overall) than patients in the OAM-only group (33.3% vs 14.4%). Insulin-only treatment was associated with significantly ($P < 0.001$) increased overall hypoglycemia compared with OAM-only treatment (odds ratio [95% confidence interval]: 2.38 [1.72, 3.29]). Sensitivity analysis

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results were consistent with the primary analysis results.

Conclusions: The results of this analysis provide important real-world information on glycemic control and hypoglycemia in Chinese patients with T2DM, which may be useful for guiding evidenced-based management. Notably, Chinese patients with T2DM receiving OAM-only had poorer glycemic control compared with those receiving insulin-only therapy, although patients receiving OAM-only were less likely to experience hypoglycemic events.

Keywords: China; Insulin; Oral antihyperglycemic medication; Type 2 diabetes mellitus

INTRODUCTION

Diabetes is a significant and growing public health issue in China. Indeed, recent estimates suggest that there are over 100 million Chinese adults with diabetes [1], nearly 500 million with prediabetes [1], and that there will be more than 140 million Chinese adults with diabetes by 2035 [2]. Worryingly, a high proportion (approximately 60%) of Chinese adults with diabetes remains unaware of their condition and those that are diagnosed tend to have inadequate glycemic control [1]. Specifically, only 41.1% of patients with type 2 diabetes mellitus (T2DM) were found to have glycated hemoglobin (HbA1c) <7.0% (<53 mmol/mol) in the Diabcare China study [3]. In another (cross-sectional hospital-based) study, 12.1% to 15.3% of patients were found to have HbA1c <6.5% (48 mmol/mol) [4]. Unsurprisingly, given that many patients have poor glycemic control, the morbidity and mortality associated with diabetes in China is significant, as indicated by the high proportion (over 50%) of patients who have chronic diabetes-related complications [4] and by the fact that diabetes is one of the major causes of death [5]. Clearly, optimizing treatment strategies will become increasingly important as the population of Chinese patients with diabetes continues to grow.

The current Chinese guidelines for the prevention and treatment of T2DM [6] state that lifestyle interventions are fundamental for the treatment of T2DM. The current glycemic target for the majority of Chinese patients with T2DM is HbA1c <7%, with testing performed every 3 months [6]. In cases where blood glucose levels cannot be controlled by lifestyle interventions only, the initiation of medical treatment is recommended. To this end, metformin is the recommended first-line treatment, followed by second-line treatment with a combination of two oral antihyperglycemic medications (OAM), third-line treatment with three OAMs or two OAMs plus insulin (basal or premixed analog), and fourth-line/intensive treatment with basal plus mealtime insulin or a premixed analog. Currently, the most common regimens used to treat T2DM in China are OAM only, insulin only, or OAM plus insulin [3, 7]. Identifying means of improving glycemic control in Chinese patients with T2DM on these regimens is key to preventing diabetes-related complications and morbidities. To date, there is little information in the published literature on differences in glycemic control between Chinese patients with T2DM receiving insulin-only and those receiving OAM-only treatment regimens, or on how patient characteristics affect glycemic control with these regimens. The information that is available comes from cross-sectional, prospective, or registry studies (carried out in mainland China [7, 8] and Hong Kong [9]) that did not perform adjustments for potentially confounding patient characteristics. The availability of appropriately adjusted, real-world data may help facilitate the development of evidence-based treatment strategies for improving glycemic control in Chinese patients with T2DM.

The primary aim of this analysis was to explore whether glycemic control (HbA1c <7%) and the incidence of hypoglycemia are different between Chinese patients with T2DM receiving OAM-only and those receiving insulin-only treatment regimens after adjusting for key patient characteristics. The secondary aim of this analysis was to explore which factors were associated with glycemic control and the incidence of hypoglycemia, respectively. We did not include patients receiving concomitant OAM and insulin treatment regimens in our analyses because regimens for this combination can be highly variable between patients, making it difficult to identify the distinct treatment effects of OAM and insulin individually or separately.

METHODS

Survey Administration

The Adelphi Real World Disease Specific Programme (DSP) is a large, cross-sectional survey of physicians and patients in a real-world clinical setting, which uses representative sampling of treated adult patients for quantification of national disease burden and assessment of treatment patterns and outcomes [10]. The DSP provides a holistic picture of a disease and treatment of that disease; the full methodology of the DSP has been published previously [11, 12].

The Diabetes DSP was carried out in China from October 2011 to March 2012 in accordance with European Pharmaceutical Marketing Research Association guidelines. Physicians were reimbursed for their participation by local fieldwork partners at fair-market rates. DSP fieldwork teams adhered to national data collection regulations.

Survey Distribution

Physicians treating patients with T2DM at general hospitals in Beijing, Shanghai, Guangzhou, Hangzhou, Nanjing, Chengdu, Wuhan, Shenyang, and Xi'an were invited to participate. These physicians were identified by local fieldwork teams from public lists according to predefined selection criteria. Specifically, physicians who had qualified between 1973 and 2009, were actively involved in diabetes management, and saw 25 or more (internal medicine physicians) or 50 or more (diabetologists and endocrinologists) patients with diabetes in a typical week were eligible to participate. Those who agreed to participate were sent physician-report forms [12] for completion. Completed surveys were collected by local fieldwork teams and returned to Adelphi Real World.

Survey Design

The survey was designed by Adelphi Real World in consultation with their local fieldwork partner in China. The physician-report form was self-administered, used clinical terminology, maintained patients' anonymity, and was confidential. All questions were originally written in English and translated into Simplified Chinese by the fieldwork partner. The translated version of the physician-report form was linguistically validated by a second independent native Chinese translator agency.

Physician-Report Form

The physician-report form collected information on patients' demographics, clinical characteristics, clinical management and outcomes (including glycemic control and hypoglycemia [chart review was necessary]), diabetes medication use and history, and physician rationale for treatment choices. The physician-report form also collected information on compliance with diabetes medication (rated by physicians as not at all, poor, fair, or full), physical activity (recorded by physicians as not at all, fairly, very, or extremely active), and lifestyle changes (recorded by physicians as no changes, some changes, many changes, or totally changed).

To answer some of the more clinical and in-depth questions, the majority of physicians would have had to refer to medical records, in which patients' medical histories, including medication history from different hospitals or physicians would be accurately recorded.

Participating physicians were those most commonly responsible for treating patients with T2DM in China, namely internal medicine physicians, diabetologists, or endocrinologists. Internal medicine physicians were asked to complete physician-report forms for the next nine consecutive patients receiving non-insulin medication with or without insulin regimens and the following two forms for consecutive patients receiving insulin-only regimens. Diabetologists and endocrinologists were asked to complete physician-report forms for the next eight consecutive patients receiving non-insulin medication with or without insulin regimens and the following two forms for consecutive patients receiving insulin-only regimens. The physician-report form quotas per physician for each regimen were based on the prevalence of T2DM in China and the duration of the survey.

Analysis Population

The population for this analysis included patients with T2DM receiving OAM-only or insulin-only treatment regimens for at least 6 months who had most recent HbA1c results available and measured within 3 months of survey completion. Patients were required to be on these regimens for at least 6 months to ensure that the HbA1c result obtained reflected average plasma glucose concentrations during a period of consistent treatment.

Outcomes (OAM-Only vs Insulin-Only)

The primary outcome was glycemic control, defined as HbA1c $<7\%$ and determined using the most recent HbA1c test result (assessed at the treating hospital) within 3 months of the survey date.

The secondary outcome was hypoglycemia, defined as any hypoglycemic episode that occurred on the treatment regimen. Hypoglycemic episodes were solicited by physicians from patients and were categorized by incidence as overall, severe, and nocturnal. Patients were provided with practical definitions of hypoglycemia. Mild hypoglycemic episodes were those that were treated by the patient by eating fruit, fruit juice, sweets, etc. Severe hypoglycemic episodes were those where the patient required third party or medical assistance. Hypoglycemia was not confirmed by blood glucose measurement.

As an exploratory, composite outcome, the proportion of patients attaining the HbA1c target $<7\%$ without hypoglycemia was also determined.

Statistical Analysis

The patients' characteristics were compared between the OAM-only and insulin-only groups by Wilcoxon rank sum test for continuous variables or Fisher's exact test for categorical variables.

The primary analysis of the primary, secondary, and composite outcomes comprised multivariate logistic regression analysis, with adjustments for age, duration since diagnosis of diabetes, education (less than high school vs. at least high school), dietary adaption (no/some changes vs. many changes/totally changed), physical activity (not at all/fairly active vs. very/extremely active), body mass index (BMI), current employment/student status (yes vs. no), treatment compliance (not at all/poorly vs. fairly/fully compliant), and self-monitoring of blood glucose concentrations (yes vs. no).

Sensitivity analysis of the primary and secondary outcomes was carried out using the propensity score (PS) matching method, which generated matched pairs to balance the patients' characteristics between the two groups. All unbalanced characteristics were included in the PS model. A 1:1 (OAM-only: insulin-only) greedy matching algorithm without replacement and with a specified caliper distance (<0.2 standard deviations of the logit of the PS) were used to identify the matched pairs. The balance of the matched treatment groups was determined by assessing the standardized difference, which compares the difference in means in units of the pooled standard deviation. A standardized difference <0.1 was taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups [13]. After matching, a generalized estimating equation (GEE) model with binomial distribution and logit link function was used to compare outcomes between the treatment groups.

A two-sided significance level of 0.05 was used for all analyses, which were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Adjustments for multiplicity were not made due to the exploratory nature of the analyses.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Analysis Population

A total of 200 physicians completed 2060 physician-report forms. Of these physician-report forms, 599 were excluded from the analyses for the following reasons (note: some forms may have had multiple reasons for exclusions): HbA1c not tested within 3 months, $n = 360$; received medication for <6 months, $n = 262$; and time since diagnosis not available, $n = 39$. Of the remaining 1461 physician-report forms, 1077 were for patients receiving OAM-only regimens, 292 were for patients receiving insulin-only regimens, and 92 were for patients receiving OAM and insulin regimens. The patients receiving OAM and insulin regimens were excluded, leaving 1369 patients on OAM-only or insulin-only regimens for inclusion in the analysis population.

Patient Characteristics

There were several significant differences in patient characteristics between the OAM-only and insulin-only groups (Table 1). Specifically, patients in the OAM-only group were younger, more recently diagnosed with T2DM, more frequently employed/students, more physically

Table 1 Characteristics of Chinese patients with T2DM by treatment regimen (OAM only vs insulin only)

Characteristic	OAM only $n = 1077$	Insulin only $n = 292$	Total $n = 1369$	*P* value[a]
Age (years)				
Mean (SD)	56.2 (10.8)	57.9 (11.0)	56.5 (10.8)	
Median (Q1, Q3)	56 (49, 63)	57 (50, 65)	56 (49, 64)	0.029
Male sex, *n* (%)	505 (46.9)	128 (43.8)	633 (46.2)	0.390
BMI (kg/m^2)				
Mean (SD)[b]	24.4 (3.1)	24.1 (2.7)	24.3 (3.0)	
Median (Q1, Q3)	24.1 (22.0, 26.1)	23.7 (22.2, 26.0)	24.0 (22.1, 26.1)	0.338
Time since diagnosis of T2DM (years)				
Mean (SD)	3.2 (3.0)	4.3 (4.5)	3.4 (3.4)	
Median (Q1, Q3)	2 (1, 4)	3 (2, 5)	2 (1, 4)	<0.001
Education level, *n* (%)[c]				0.204
Less than high school	253 (24.8)	75 (28.7)	328 (25.6)	
At least high school	766 (75.2)	186 (71.3)	952 (74.4)	
Currently employed/student, *n* (%)[d]	441 (41.0)	95 (32.6)	536 (39.2)	0.010
Current smoker, *n* (%)[e]	150 (14.4)	34 (11.9)	184 (13.9)	0.333
Treatment compliant[f], *n* (%)[g]				0.327
Not at all/poorly	183 (17.1)	42 (14.5)	225 (16.6)	
Fairly/fully	887 (82.9)	247 (85.5)	1134 (83.4)	
Dietary adaptation, *n* (%)[h]				0.891
No/some changes	397 (36.9)	106 (36.3)	503 (36.8)	
Many changes/totally changed	679 (63.1)	186 (63.7)	865 (63.2)	
Physically active, *n* (%)[i]				0.022
Not at all/fairly	138 (12.8)	53 (18.2)	191 (14.0)	
Very/extremely	938 (87.2)	238 (81.8)	1176 (86.0)	
Self-monitored blood glucose (yes), *n* (%)[j]	403 (41.0)	198 (70.7)	601 (47.5)	<0.001

BMI body mass index, *OAM* oral antihyperglycemic medication, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *T2DM* type 2 diabetes mellitus

[a] Continuous variables were compared between the OAM-only and insulin-only groups by Wilcoxon rank sum test. Categorical variables were compared between these groups by Fisher's exact test

[b] Missing data (*n*): OAM = 4, insulin = 2

[c] Missing data (*n*): OAM = 58, insulin = 31

[d] Missing data (*n*): OAM = 1, insulin = 1

[e] Missing data (*n*): OAM = 34, insulin = 7

[f] Rated by physicians as not at all, poorly, fairly, or fully compliant

[g] Missing data (*n*): OAM = 7, insulin = 3

[h] Missing data (*n*): OAM = 1

[i] Missing data (*n*): OAM = 1, insulin = 1

[j] Missing data (*n*): OAM = 93, insulin = 12

active, and less commonly self-monitored blood glucose concentrations than patients in the insulin-only group (all $P < 0.05$). A high proportion (>80%) of patients in both groups were fairly or fully compliant with treatment according to physicians' ratings.

Using the PS matching method to balance the characteristics of two treatment groups, a total of 474 patients (237 per treatment group) were successfully matched. All patient characteristics were well balanced (all $P > 0.2$; standardized difference <0.1) (Table 2; Fig. 1). Thus, matched patients from the 2 treatment groups were similar and appropriate for use in the sensitivity analysis.

Glycemic Control

Primary Analysis

Without any adjustment, a higher proportion of patients in the insulin-only group achieved glycemic control (HbA1c <7%) than patients in the OAM-only group (41.8% [122/292] vs 35.9% [387/1077]). After adjusting for potential confounding factors, insulin-only treatment was associated with significantly better glycemic control (odds ratio [OR] [95% confidence interval {CI}]): 1.48 [1.09, 2.01], $P = 0.013$) than OAM-only treatment (Fig. 2). Other factors that were associated with significantly better glycemic control included a shorter time since diagnosis of T2DM (OR [95% CI]: 0.87 [0.83, 0.92], $P < 0.001$), dietary adaptation involving many changes or total changes (OR [95% CI]: 2.33 [1.78, 3.04], $P < 0.001$), physical activity defined as very/extremely active (OR [95% CI]: 2.16 [1.42, 3.29], $P < 0.001$), a BMI of 24.0–27.9 kg/m^2 (OR [95% CI]: 1.44 [1.11, 1.86], $P = 0.006$), and treatment compliance (OR [95% CI]: 3.26 [2.14, 4.96], $P < 0.001$).

Sensitivity Analysis

A total of 237 paired patients were included in the sensitivity analysis. The results of the sensitivity analysis for glycemic control were consistent with the results of the primary analysis. A higher proportion of patients in the insulin-only group achieved glycemic control (HbA1c <7%) than patients in the OAM-only group (47.3% [112/237] vs 38.0% [90/237]). The GEE model showed that insulin-only treatment was associated with significantly better glycemic control than OAM-only treatment (OR [95% CI]: 1.46 [1.02, 2.09], $P = 0.037$).

Hypoglycemia

Primary Analysis

Without any adjustment, a higher proportion of patients in the insulin-only group reported experiencing hypoglycemia (overall), severe hypoglycemia, and nocturnal hypoglycemia than patients in the OAM-only group (33.3% [97/291] vs 14.4% [155/1074], 8.6% [25/291] vs 1.6% [17/1074], and 16.2% [47/291] vs 7.9% [85/1074], respectively). After adjusting for potential confounding factors, insulin-only treatment was associated with significantly (OR [95% CI]: 2.38 [1.72, 3.29], $P < 0.001$) increased overall hypoglycemia compared with OAM-only treatment (Fig. 3). Other factors that were significantly (all $P < 0.01$) associated with overall hypoglycemia included a longer time since diagnosis of T2DM, dietary adaptation involving many changes or total changes, and self-monitoring of blood glucose concentrations.

Sensitivity Analysis

The results of the sensitivity analysis for hypoglycemia were consistent with the results of the primary analysis. A higher proportion of patients in the insulin-only group reported

Table 2 Propensity score matched characteristics of Chinese patients with T2DM by treatment regimen (OAM only vs insulin only)

Characteristic	OAM only $n = 237$	Insulin only $n = 237$	Total $n = 474$	P value[a]
Age (years)				
Mean (SD)	56.9 (11.6)	57.3 (10.6)	57.1 (11.1)	
Median (Q1, Q3)	56 (49, 65)	57 (50, 64)	57 (50, 64)	0.522
Male sex, n (%)	110 (46.4)	104 (43.9)	214 (45.1)	0.645
BMI (kg/m^2)				
Mean (SD)	24.2 (3.0)	24.3 (2.7)	24.2 (2.8)	
Median (Q1, Q3)	23.8 (21.9, 26.0)	23.9 (22.5, 26.2)	23.9 (22.2, 26.1)	0.258
Time since diagnosis of T2DM (years)				
Mean (SD)	3.8 (3.7)	3.8 (3.5)	3.8 (3.6)	
Median (Q1, Q3)	3 (2, 5)	2 (2, 5)	3 (2, 5)	0.787
Education level, n (%)[b]				0.742
Less than high school	55 (25.0)	57 (26.8)	112 (25.9)	
At least high school	165 (75.0)	156 (73.2)	321 (74.1)	
Currently employed/student, n (%)	92 (38.8)	81 (34.2)	173 (36.5)	0.340
Current smoker, n (%)[c]	25 (11.1)	27 (11.6)	52 (11.4)	0.884
Treatment compliant[d], n (%)				1.000
Not at all/poorly	30 (12.7)	30 (12.7)	60 (12.7)	
Fairly/fully	207 (87.3)	207 (87.3)	414 (87.3)	
Dietary adaptation, n (%)				0.562
No/some changes	85 (35.9)	78 (32.9)	163 (34.4)	
Many changes/totally changed	152 (64.1)	159 (67.1)	311 (65.6)	
Physically active, n (%)				0.804
Not at all/fairly	40 (16.9)	37 (15.6)	77 (16.2)	
Very/extremely	197 (83.1)	200 (84.4)	397 (83.8)	
Self-monitored blood glucose (yes), n (%)	168 (70.9)	169 (71.3)	337 (71.1)	1.000

BMI body mass index, *OAM* oral antihyperglycemic medication, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *T2DM* type 2 diabetes mellitus

[a] Continuous variables were compared between the OAM-only and insulin-only groups by Wilcoxon rank sum test. Categorical variables were compared between these groups by Fisher's exact test

[b] Missing data (n): OAM = 17, insulin = 24

[c] Missing data (n): OAM = 12, insulin = 5

[d] Rated by physicians as not at all, poorly, fairly, or fully compliant

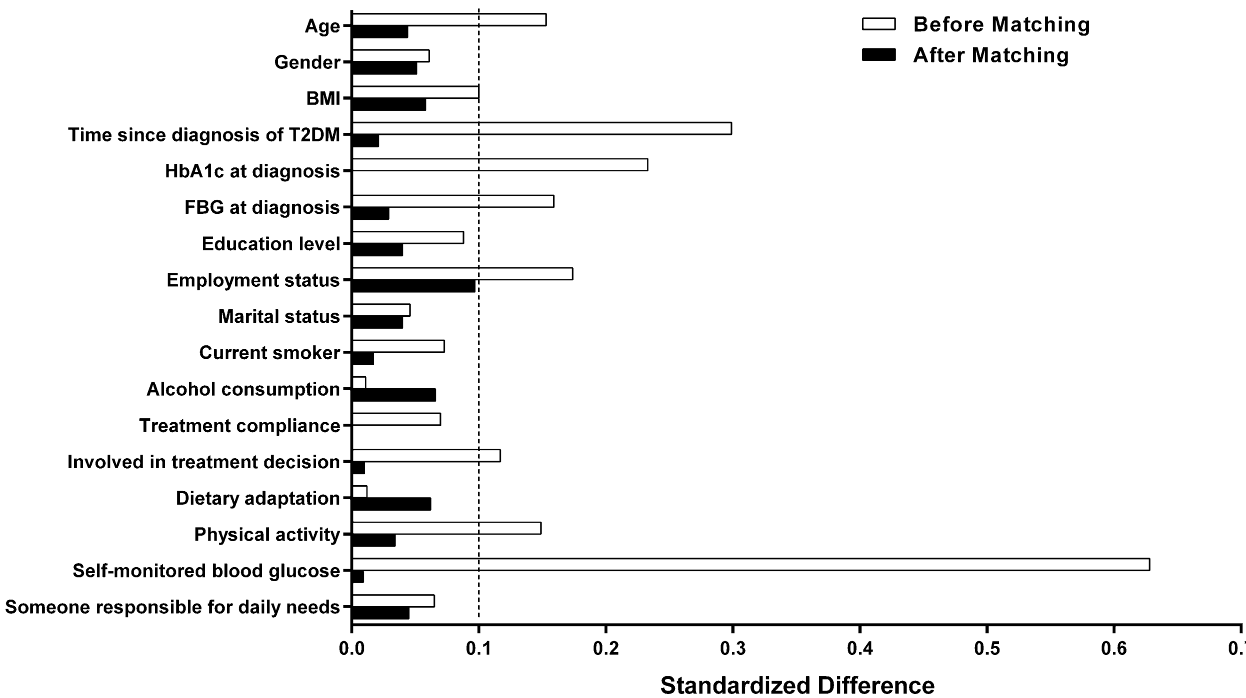

Fig. 1 Standardized differences for patient characteristics before and after propensity score matching. A standardized difference <0.1 was taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups [13]. All characteristics were well balanced (standardized difference <0.1) after propensity score matching. *BMI* body mass index, *FBG* fasting blood glucose, *HbA1c* glycated hemoglobin, *T2DM* type 2 diabetes mellitus

experiencing hypoglycemia (overall), severe hypoglycemia, and nocturnal hypoglycemia than patients in the OAM-only group (36.0% [85/236] vs 16.5% [39/237], 8.9% [21/236] vs 1.3% [3/237], and 18.6% [44/236] vs 8.4% [20/237], respectively). The GEE model showed that insulin-only treatment was associated with significantly increased overall hypoglycemia compared with OAM-only treatment (OR [95% CI]: 2.86 [1.89, 4.34], $P < 0.001$).

Glycemic Control Without Hypoglycemia

The proportion of patients attaining HbA1c <7% without hypoglycemia was similar in both groups (29.98% in the OAM-only group vs 26.46% in the insulin-only group).

Both univariate and multivariate analyses revealed that there was no association between the type of treatment and the composite outcome, HbA1c <7% without hypoglycemia ($P > 0.24$). In contrast, HbA1c <7% without hypoglycemia was significantly associated with a shorter time since diagnosis of T2DM (OR [95% CI]: 0.86 [0.81, 0.92], $P < 0.001$), many changes/totally changed diet (OR [95% CI]: 1.96 [1.47, 2.61], $P < 0.001$), very active/extremely active physical activity (OR [95% CI]: 1.72 [1.09, 2.71], $P = 0.020$), and full/fair treatment compliance (OR [95% CI]: 3.09 [1.94, 4.90], $P < 0.001$).

DISCUSSION

This is the first analysis to explore whether glycemic control is different between Chinese patients with T2DM receiving OAM-only and those receiving insulin-only treatment regimens after adjusting for key patient

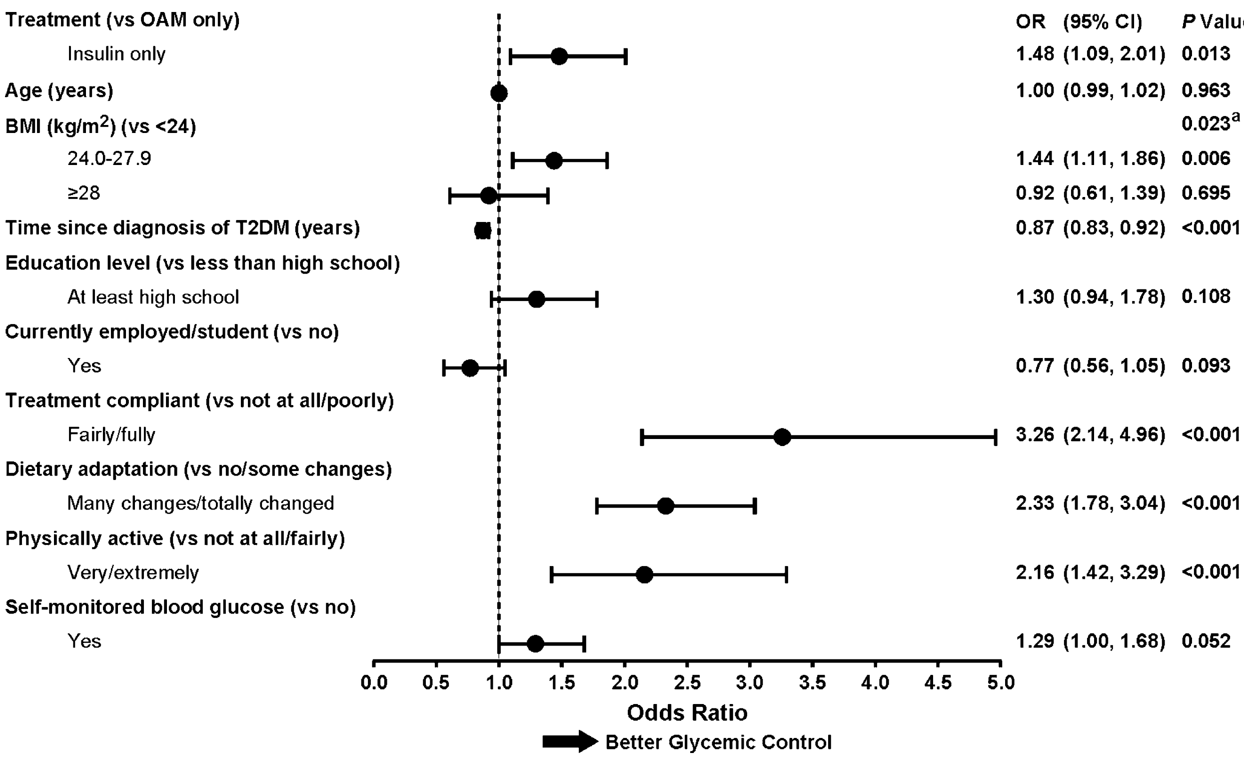

Fig. 2 Multivariate analysis of variables associated with glycemic control (glycated hemoglobin <7%) in Chinese patients with type 2 diabetes mellitus receiving oral antihyperglycemic medication-only or insulin-only treatment regimens. *BMI* body mass index, *CI* confidence interval, *OAM* oral antihyperglycemic medication, *OR* odds ratio, *T2DM* type 2 diabetes mellitus. [a]Overall *P* value for BMI (type 3 analysis of effects)

characteristics. The main findings of our analysis are that, in patients with similar core clinical and demographic characteristics, insulin-only treatment was associated with significantly better glycemic control (HbA1c <7%) than OAM-only treatment and significantly increased overall hypoglycemia compared with OAM-only treatment. We also identified several other distinct factors associated with better glycemic control, including shorter time since diagnosis of T2DM, dietary adaptation, physical activity, BMI, and treatment compliance. Several factors were also found to be associated with hypoglycemia, including insulin-only treatment, longer time since diagnosis of T2DM, dietary adaptation, and self-monitoring of blood glucose. This analysis provides important real-world information on factors affecting glycemic control and hypoglycemia in Chinese patients with T2DM, which may be useful for guiding evidenced-based management strategies.

Consistent with findings from other studies [3, 4, 14–17], we found that a relatively low proportion of Chinese patients with T2DM had adequate glycemic control (HbA1c <7%). Importantly, however, we also found that insulin-only treatment regimens may provide better glycemic control than OAM-only treatment regimens in patients with similar core clinical and demographic characteristics. Previous cross-sectional, prospective, registry, or survey studies carried out in China (mainland [7, 8] and Hong Kong [9]) and elsewhere [18, 19] comparing glycemic control between patients

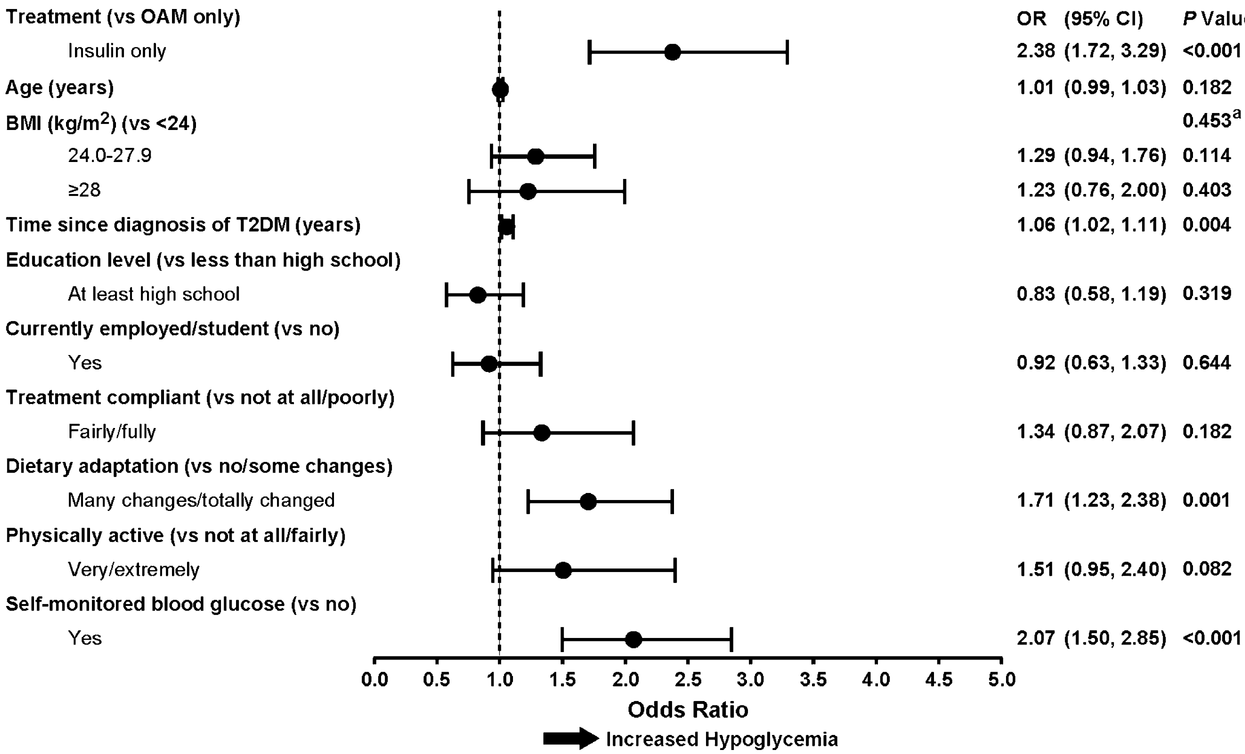

Fig. 3 Multivariate analysis of variables associated with hypoglycemia in Chinese patients with type 2 diabetes mellitus receiving oral antihyperglycemic medication-only or insulin-only treatment regimens. *BMI* body mass index, *CI* confidence interval, *OAM* oral antihyperglycemic medication, *OR* odds ratio, *T2DM* type 2 diabetes mellitus. [a]Overall *P* value for BMI (type 3 analysis of effects)

receiving insulin-only and OAM-only treatment regimens have not made these comparisons after adjustment for potentially confounding patient characteristics. In contrast to the present analysis, these previous studies found that patients receiving OAM-only treatment regimens had better levels of glycemic control than patients receiving insulin-only treatment regimens. Our findings therefore highlight the importance of adjusting for patient characteristics when evaluating glycemic control. Differences in patient cohort characteristics, in particular disease duration (generally shorter in our analysis), between our analysis and previous studies [7–9, 18, 19] may also have contributed to the different findings regarding glycemic control.

We found that a number of other factors were associated with glycemic control, including modifiable factors such as patients' dietary adaption, physical activity level, BMI, and treatment compliance, as well as the non-modifiable factor, duration of disease. These are all well-established factors known to be important in the management of T2DM/glycemic control [6, 14, 20–23]. A high level of treatment compliance, more pronounced dietary adaptation, and increased physical activity had the strongest associations with better glycemic control. Our finding regarding treatment compliance is noteworthy given that a high proportion (>80%) of patients were considered to be fairly or fully compliant by their physicians. Therefore, it is clear that

Chinese physicians and healthcare providers managing patients with T2DM have an important role to play in educating and encouraging patients to ameliorate these modifiable factors in the management of their condition.

The effective treatment of diabetes is a delicate balance between good glycemic control and managing the risk of hypoglycemia, an established risk of treatment with insulin [23, 24]. Hence, our finding that insulin-only treatment was associated with an increased incidence of hypoglycemia in Chinese patients with T2DM compared with OAM-only treatment is unsurprising. There are a number of key modifiable factors affecting this balance, including the type of medication, medication dose, glycemic control target, diet, exercise, non-diabetic drug/alcohol use, and blood glucose monitoring [25–27]. Patient-centric individualization of treatment is an important consideration [27], emphasized by the Chinese Diabetes Society, the American Diabetes Association, and the European Association for the Study of Diabetes [28, 29]. Interestingly, we found that patients who made many changes or totally changed their diet had increased hypoglycemia compared with those who made no or some changes to their diet. This finding suggests many Chinese patients with T2DM receiving insulin-only or OAM-only treatment regimens who change their diet may not understand/be aware of the importance of the relationship between diet, diabetes medication, and blood glucose concentrations. Therefore, more comprehensive patient education on diet/meal planning, including appropriate titration of insulin dosing, may be necessary. Indeed, several previous studies have demonstrated the importance of education for improving glycemic control in Chinese patients with T2DM, particularly among those who have lower incomes and/or are less educated [20, 30]. We also found that self-blood glucose measurement was associated with an increased incidence of hypoglycemia. Our analysis does not allow us to draw any conclusion regarding the direction of this relationship; hence, we suggest that patients who more commonly experienced hypoglycemia may have been more likely to measure their blood glucose concentrations, indicating the possibility of ascertainment bias in the sample. Indeed, the Chinese Diabetes Society recommends that patients with T2DM should measure their blood glucose concentrations when symptoms of hypoglycemia occur [29].

Composite outcomes have been used to assess overall disease control, including in the context of T2DM [31]. In the present analysis, we did not find any association between treatment and the composite outcome, glycemic control (HbA1c $<7\%$) without hypoglycemia. However, in agreement with the analysis of glycemic control, glycemic control without hypoglycemia was associated with several modifiable factors, including patients' dietary adaptation, physical activity level, and treatment compliance, as well as the non-modifiable factor, duration of disease. The associations between glycemic control without hypoglycemia and these modifiable factors again emphasize the importance of patients being made aware that aspects of their behavior/lifestyle can affect treatment outcomes.

This analysis has several noteworthy strengths, including the use of real-world data and the strong agreement in the results of the primary and sensitivity analyses. Limitations include that data were obtained from patients being treated in a selected number of medium or large cities (hence, the results may not be applicable to the larger [non-urban] Chinese population); that several factors (e.g., hypoglycemia and treatment compliance) were not objectively assessed; and that the cross-sectional design does not allow for assessment of the effect of T2DM treatment regimens or compliance on longitudinal glycemic control at the time of the survey. Although the assessments of hypoglycemia and treatment compliance were not objective, it must be emphasized that the means of assessment described are widely used in real-world clinical practice in China and therefore drive treatment decisions.

CONCLUSION

In summary, the main finding of our analysis is that insulin-only treatment was associated with better glycemic control than OAM-only treatment in Chinese patients with T2DM. This is an important finding given that glycemic control is essential for preventing diabetes-related complications and that many patients with T2DM in China have inadequate glycemic control. Prospective studies are needed to further explore this finding and determine, considering the increased risk of hypoglycemia, whether certain subsets of Chinese patients with T2DM may benefit from insulin-only treatment rather than OAM-only treatment. Studies are also needed to determine which potentially modifiable factors targeted for specific interventions may improve outcomes for patients on these regimens.

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REFERENCES

1. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. JAMA. 2013;310:948–59.

2. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels: International Diabetes Federation; 2013.

3. Pan C, Yang W, Jia W, Weng J, Tian H. Management of Chinese patients with type 2 diabetes, 1998-2006: The Diabcare-China surveys. Curr Med Res Opin. 2009;25:39–45.

4. Liu Z, Fu C, Wang W, Xu B. Prevalence of chronic complications of type 2 diabetes mellitus in outpatients—a cross-sectional hospital based survey in urban China. Health Qual Life Outcomes. 2010;8:62.

5. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2013;381:1987–2015.

6. Chinese Diabetes Society. China T2DM Prevention and Treatment Guideline (2013). Chin J Diabetes Mellitus. 2014;6:447–98.

7. Bi Y, Zhu D, Cheng J, Zhu Y, Xu N, Cui S, et al. The status of glycemic control: a cross-sectional study of outpatients with type 2 diabetes mellitus across primary, secondary, and tertiary hospitals in the Jiangsu province of China. Clin Ther. 2010;32:973–83.

8. Wang JF, Luo BY. Analysis of the antidiabetic therapy in type 2 diabetes mellitus patients in suburban community. Clin Ration Drug Use. 2012;5:1–2.

9. Tong PC, Ko GT, So WY, Chiang SC, Yang X, Kong AP, et al. Use of anti-diabetic drugs and glycaemic control in type 2 diabetes—The Hong Kong Diabetes Registry. Diabetes Res Clin Pract. 2008;82:346–52.

10. Babineaux SM, Curtis B, Holbrook T, Liu L, Colclough H, Piercy J. Evidence for validity of a national physician and patient-reported survey in China and UK: The Disease Specific Programme. ISPOR 6th Asia-Pacific conference, Beijing, China; 2014.

11. Anderson P, Benford M, Harris N, Karavali M, Piercy J. Real-world physician and patient behaviour across countries: Disease-Specific Programmes—a means to understand. Curr Med Res Opin. 2008;24:3063–72.

12. Benford M, Milligan G, Pike J, Anderson P, Piercy J, Fermer S. Fixed-dose combination antidiabetic therapy: real-world factors associated with prescribing choices and relationship with patient satisfaction and compliance. Adv Ther. 2012;29:26–40.

13. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46:399–424.

14. Li MZ, Ji LN, Meng ZL, Guo XH, Yang JK, Lu JM, et al. Management status of type 2 diabetes mellitus in tertiary hospitals in Beijing: gap between guideline and reality. Chin Med J (Engl). 2012;125:4185–9.

15. Ji LN, Lu JM, Guo XH, Yang WY, Weng JP, Jia WP, et al. Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. BMC Public Health. 2013;13:602.

16. Li C, Wang A, Zhang Y, Ning X, Lei M. Knowledge of blood sugar control standard brings the higher attainment rate of HbA1c. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2013;38:773–8.

17. Ji LN, Lu JM, Guo XH, Yang WY, Weng JP, Jia WP, et al. Status of blood glucose control and treatment of type 2 diabetes in China. Chin J Diabetes Mellitus. 2012;4:397–401.

18. Dodd AH, Colby MS, Boye KS, Fahlman C, Kim S, Briefel RR. Treatment approach and HbA1c control among US adults with type 2 diabetes: NHANES 1999–2004. Curr Med Res Opin. 2009;25:1605–13.

19. Norkus A, Ostrauskas R, Zalinkevicius R, Radzeviciene L, Sulcaite R. Adequate prescribing of medication does not necessarily translate into good control of diabetes mellitus. Patient Prefer Adher. 2013;7:643–52.

20. Guo XH, Yuan L, Lou QQ, Shen L, Sun ZL, Zhao F, et al. A nationwide survey of diabetes education,

self-management and glycemic control in patients with type 2 diabetes in China. Chin Med J (Engl). 2012;125:4175–80.

21. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA. 2001;286:1218–27.

22. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. Clin Ther. 2011;33:74–109.

23. Standards of medical care in diabetes. 2014. Diabetes Care. 2014;37(suppl 1):S14–80.

24. Anderson M, Powell J, Campbell KM, Taylor JR. Optimal management of type 2 diabetes in patients with increased risk of hypoglycemia. Diabetes Metab Syndr Obes. 2014;7:85–94.

25. Ahren B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. Vasc Health Risk Manag. 2013;9:155–63.

26. Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach KN, Ryan GJ, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med. 2014;174:678–86.

27. McCall AL. Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am. 2012;41:57–87.

28. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55:1577–96.

29. Chinese Diabetes Society. China guideline for type 2 diabetes. Chin J Diabetes Mellitus. 2010;2(suppl 2):6–56.

30. Guo XH, Ji LN, Lu JM, Liu J, Lou QQ, Shen L, et al. Efficacy of structured education in patients with type 2 diabetes mellitus receiving insulin treatment. J Diabetes. 2014;6:290–7.

31. Zinman B, Schmidt WE, Moses A, Lund N, Gough S. Achieving a clinically relevant composite outcome of an HbA1c of <7% without weight gain or hypoglycaemia in type 2 diabetes: a meta-analysis of the liraglutide clinical trial programme. Diabetes Obes Metab. 2012;14:77–82.